REMARKS

Claims 63-76, and 90-145 are pending in the application. Claims 77-89 and 146-147 are cancelled herein, without prejudice, in accordance with the Restriction Requirement Paper No. 10, as noted above. Claims 64-76, 91, 92, 95-99, 102, 104-113, 125, 126, 128, 130, 132, and 134-145 are withdrawn from examination as directed to non-elected species, and their future rejoinder upon allowance of generic subject matter to these species is expected. Claims 63, 90, 93-94, 100, 101, 103, 114-124, 127, 129, 131, and 133 are under examination on the merits to the extent that they read on the elected species noted in the record. With entry of this amendment, claims 117 and 122-124 have been amended for clarity in accordance with the Office's suggestions. The subject amendments are fully supported by the disclosure and no new matter has been added to the application.

Claim Objections:

Applicants acknowledge that the Office has reconsidered and withdrawn the objections to claims 101 and 114.

Patentability Under 35 U.S.C. § 112, Second Paragraph:

Applicants acknowledge that the Office has reconsidered and withdrawn the former rejections of claims 90 and 115-116 under 35 U.S.C. § 112, Second Paragraph.

Patentability Under 35 U.S.C. § 112, First Paragraph:

Claim 101 is rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that is not enabled by the disclosure. This rejection is directed to a deposit requirement, and the Examiner has called for Applicants to submit evidence that the necessary deposits have been made under Budapest conditions, and to amend the specification to refer to the deposit. Applicants forwarded official Certifications of the subject deposit on March 25th, 2002 showing that the requested deposits were made and formal requirements met. Applicants will provide under separate coverage an appropriate Declaration of Dr. Brian R. Murphy relating to the deposited material. The specification already discloses the pertinent information relating to the deposit. On this basis,

withdrawal of the rejection of claim 101 under 35 U.S.C. § 112, first paragraph is earnestly solicited.

Claims 117-124 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office focused on specific language of the claims reciting "vaccine compositions to induce protection against RSV" and challenged that such specific efficacy of the subject compositions is allegedly not enabled.

Applicants respectfully traverse the stated grounds for rejection and submit that the specification fully enables production of live-attenuated RSV vaccines capable of eliciting a protective immune response in human subjects. In this regard, Applicants rely on the detailed facts and remarks presented in their prior Amendment/Response filed March 25th, 2001, incorporated herein by reference.

The instant rejection, however, is obviated by Applicants' clarifying amendments to the claims herein. The claims no longer specifically recite a "vaccine" composition that is necessarily effective "to induce protection against RSV." Rather, the amended claims recite "[a]n immunogenic composition effective to elicit an immune response in a mammalian subject directed against RSV." Thus, the amended claims embrace compositions having a variety of corresponding uses, including for example laboratory and clinical diagnostic uses, screening uses, and various immunization methods, including human vaccine uses.

To evaluate enablement of these amended claims, the Office's attention is respectfully directed to the Training Materials for Examining Patent Applications With Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications (hereinafter "Enablement Guidelines"), at Section Sec. III(A)(2)):

> [W]hen a compound or composition claim is not limited by a recited use, **any** enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention (emphasis supplied).

In the instant case, the claims no longer recite a specific use limitation for the claimed compositions as a "protective" "vaccine", and the subject compositions are clearly enabled for a number of different uses commensurate with the claims presented for review. Accordingly, withdrawal of the rejection of claims 117-124 under 35 U.S.C. § 112, first paragraph, is earnestly solicited.

Patentability Under 35 U.S.C. § 103:

Claims 63, 93, 94, 114, 115, 117, 121-124, 127, 131, and 133 are rejected under 35 U.S.C. § 103 as allegedly obvious over Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al. The Office initially relied upon Collins et al. (see former Office Action, Paper No. 12) for allegedly teaching "infectious recombinant RSV . . . wherein defined changes can be introduced for development of live attenuated vaccine strains" (Id., at p. 9). In addition, the Office initially argued that "Collins teaches that mutations can be introduced that ablate or reduce the level of expression of specific proteins", and that "ablation or modification of specific genes may result in attenuated RSV vaccine strains with enhanced immunogenicity and a higher level of protection against RSV than wild-type virus." The Office conceded that Collins fails to teach modification or ablation of specific genes by introduction of a translation termination codon. However, the Office relied on any of Marr et al., Chen et al., or Doyle et al for teaching a general concept of "mutagenesis of viral genomes by introduction of one or more translation termination codons in order to reduce or ablate expression of specific proteins." On this basis, the Office asserted that it would have been obvious to mutagenize a viral genome by introduction of one or more translation termination codons to reduce or ablate gene expression "for generation of attenuated recombinant RSV suitable for use as a vaccine strain."

Thus, the position originally advocated by the Office was that Collins et al. actually discloses RSV having defined changes "for development of live attenuated vaccine strains", and that the reference further teaches RSV with ablated or modified genes that can yield "attenuated RSV vaccine strains with enhanced immunogenicity and a higher level of protection against RSV."

This initial characterization presented by the Office concerning the teachings of Collins et al. appears to now be withdrawn. In the current Office Action, the Examiner

seems to propose that, even if no practical results for developing a useful vaccine candidate were reasonably expected based on the Collins et al. teachings, the reference would still enable a recombinant RSV having "defined changes" (Office Action Paper No. 18, at p. 4). This redacted view clearly contravenes governing legal authority.

Long established case law makes it clear that a reference relied upon under 35 U.S.C. § 103 must provide a practical motivation to make a claimed invention, which generally requires a reasonable expectation of success that the invention will yield the "particular results" disclosed in an Applicants' specification. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 U.S.P.Q.d 543 (Fed. Cir. 1985). The Feil court explained this test as requiring a suggestion that a particular combination "could achieve the advantages of (the claimed invention)."

The particular results that support a suggestion or motivation to make a claimed invention must be provided by the cited reference, but they need not be specifically recited in the claims under review, contrary to the Office's assertion (see Paper No. 17, at p. 4—stating that the claims under review are not limited to protective vaccines). This is clear from the Federal Circuit's reasoning in In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529 (1988):

> There must be a reason or suggestion in the art for selecting the (combination), other than the knowledge learned from the applicant's disclosure.

To determine whether a reference provides a reasonable expectation of success for achieving the desired results of a particular invention, the Federal Circuit's predecessor court stated in In re Gyurik, 201 USPQ 552, 557 (CCPA 1979) as follows:

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.

Thus, a reliable reference under 35 U.S.C. § 103 must not only suggest the claimed compound or composition (e.g., a recombinant RSV modified as claimed--specifically exemplified by RSV with a gene knock-out achieved by introduction of one or more translation termination codons), but must also reasonably forecast the properties

that the skilled artisan would expect this new compound or composition to have if it was in fact successfully made.

In the instant case, the Collins et al. reference does not show successful recovery of a recombinant RSV having any genome modification as claimed. Moreover, the reference fails to establish that a recombinant RSV having a genome modification as claimed would be expected to possess such critical properties as replication competence, infectivity, immunogenicity, and attenuation *in vivo*. Therefore, the reference fails to provide the requisite "practical motivation" and specific guidance to raise the disclosure beyond what the courts have uniformly characterized as an "obvious to try" teaching—or "an invitation to experiment." As articulated by the District Court in Merck and Co. Inc. v. Danbury Pharacal, Inc., 8 USPQ2d 1793, 1816 (D. Del. 1988) (quoting and citing, respectively, In re Fine, 5 USPQ2d 1596, 1599, (Fed. Cir. 1988), and In re Merck, 231 USPQ 375, 379-80 (Fed. Cir. 1986)):

> [T]he governing standard is emphatically not whether a particular method or process leading to an invention would be "obvious to try", but whether such an experiment would have been expected to succeed.

The Collins et al. reference clearly reflects an "obvious to try" disclosure when viewed in accordance with this legal authority. In particular, Collins and coworkers expressly qualify the limitations of their report, in the very portion relied upon by the Examiner, as follows:

> The ability to introduce defined mutations into infectious RSV should have many applications in extending analyses of RSV molecular biology and pathogenesis. For example, the functions of the RSV proteins, especially the NS1, NS2, SH, M2(ORF1), and M2(ORF2) proteins, could be investigated by introducing mutations that ablate or reduce their level of expression or that yield mutant protein. (p. 11156, left column last paragraph, bridging to right column, emphasis supplied).

In other passages, Collins and coworkers further clarify the hypothetical nature of their discussion, as follows:

> An exciting possibility is that RSV might be engineered in ways that enhance its immunogenicity and induce a level of protection greater than that provided by natural infection." (page 11167, left column, last paragraph).
>
> ***

> Also, it should be possible to explore other methods of attenuation. (page 11165, right column, last partial paragraph).

These collective expressions--"should have many applications", "could be investigated", "exciting possibility", "might be engineered", and "should be possible to explore"--clearly indicate that the Collins et al. report provides no more than an invitation to experiment. It therefore cannot be fairly concluded on the present record that a skilled artisans would have viewed the Collins disclosure as providing a "reasonable expectation of success" for making a recombinant RSV having a genome modification as claimed (and represented in the elected species by a gene knock out engineered by introduction of one or more translation termination codons) that would retain, or acquire, the particular characteristics described by Applicants.

Only with the benefit of hindsight based on Applicants' detailed disclosure is it reasonable to predict that a recombinant RSV having a genome modification as claimed is recoverable from cDNA as a self-replicating, infectious, immunogenic, and attenuated construct which would be useful within immunogenic compositions as presently claimed. Without the benefit of Applicants' disclosure, Collins et al. simply suggest that defined mutations may be introduced into a recombinant RSV. The reference speculates regarding a large laundry list of possible permutations in recombinant RSV, but notably fails to provide working examples of any actual constructs, nor evidence of their expected viability and immunological characteristics. This factual scenario squarely fits the nonobviousness analysis provided by the Federal Circuit in In re O'Farrell,

> [i]n some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication or which parameters were critical or no direction as to which of many possible choices is likely to be successful." 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

In view of the foregoing evidence and authority, Applicants respectfully request that the rejection of claims 63, 93, 94, 114, 115, 117, 121-124, 127, 131, and 133 are rejected under 35 U.S.C. § 103 as allegedly obvious over Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al. be withdrawn The general alleged teachings of

Marr et al., Chen et al., and Doyle et al. regarding mutagenesis of viral genomes do not cure the deficiencies of the Collins et al. primary reference noted above. The Collins et al. disclosure fails to provide a reasonable expectation of success for making a viable, infectious, immunogenic RSV from cDNA having a genome modification as claimed. It is even more speculative to extrapolate beyond Collins' limited disclosure to incorporate general teachings from the cited secondary references with an expectation of achieving the successful results first disclosed in Applicants' specification.

Claims 90, 100, 101, and 103 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al. and further in view of any of Crowe et al. #1, Crow et al. #2 Crowe et al., 1995, or Murphy et al. Collins et al. is relied upon by the Office as the primary reference, and Marr et al., Chen et al., and Doyle et al. as secondary references, as set forth above. Crowe et al. #1, Crow et al. #2 Crowe et al., 1995, and Murphy et al. are each relied upon for teaching certain biologically derived mutant RSV strains (Office Action Paper No. 12, at p. 11). Combining these alleged teachings, the Office contends that it would have been obvious to incorporate attenuating mutations present in one or more of these biologically derived mutant strains "to further attenuate the infectious recombinant RSV taught by Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al."

Applicants respectfully traverse this rejection on the basis that Collins et al. is a defective primary reference for the reasons set forth in detail above. The general alleged teachings of Marr et al., Chen et al., and Doyle et al. regarding mutagenesis of viral genomes do not cure the deficiencies of the Collins et al. reference. It is even more speculative to extrapolate beyond Collins' limited disclosure, viewed in combination with Marr et al., Chen et al., or Doyle et al., to incorporate yet additional teachings relating to biologically derived mutant RSV, with the further goal of achieving a more attenuated recombinant RSV as disclosed in Applicants' specification. Accordingly, the rejection of claims 90, 100, 101, and 103, as rejected under 35 U.S.C. 103(a) over Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al. and further in view of any of Crowe et al. #1, Crow et al. #2 Crowe et al., 1995, or Murphy et al., is believed to be overcome.

Claims 116, 118-120, 123, and 124 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Collins et al. in view of any of Marr et al., Chen et al., or

Doyle et al. and further in view of Randolph et al. Collins et al. is relied upon by the Office as the primary reference, and Marr et al., Chen et al., and Doyle et al. as secondary references, as set forth above. Randolph et al. is cited for teaching intranasal administration of an aerosol containing 10^6 PFU of attenuated infectious RSV for eliciting systemic immunity. Combining these alleged teachings, the Office contends that it would have been prima facie obvious to administer the recombinant RSV taught by Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al. via the dosage and route taught by Randolph et al.

Applicants respectfully traverse this rejection on the basis that Collins et al. is a defective primary reference for the reasons noted above. The general alleged teachings of Marr et al., Chen et al., and Doyle et al. regarding mutagenesis of viral genomes do not cure the deficiencies of the Collins et al. reference. It is even more speculative to extrapolate beyond Collins' limited disclosure, viewed in combination with Marr et al., Chen et al., or Doyle et al., to incorporate yet additional teachings relating to successful dosage and route of administration for RSV immunization as disclosed by Applicants. Withdrawal of the rejection of claims 116, 118-120, 123, and 124 are under 35 U.S.C. 103(a) is therefore earnestly solicited.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version With Markings To Show Changes Made."

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 425-455-5575.

Respectfully submitted,

Date: 4/29/03

Jeffrey J. King
Registration No. 38,515

VERSION WITH MARKINGS TO SHOW CHANGES MADE

63. (Original) An isolated infectious recombinant respiratory syncytial virus (RSV) comprising a RSV genome or antigenome, a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase protein (L), and a RNA polymerase elongation factor, wherein a modification is introduced within the genome or antigenome comprising a deletion, insertion, substitution, rearrangement, or nucleotide modification of a cis-acting regulatory sequence within the recombinant RSV genome or antigenome.

64. (Withdrawn) The recombinant RSV of claim 63, wherein the cis-acting regulatory sequence is a gene-start (GS) signal or a (GE) signal.

65. (Withdrawn) The recombinant RSV of claim 64, wherein a GS or GE signal is deleted or inserted in the genome or antigenome.

66. (Withdrawn) The recombinant RSV of claim 64, wherein a GS or GE signal is substituted in the genome or antigenome by a heterologous GS or GE sequence.

67. (Withdrawn) The recombinant RSV of claim 66, wherein the heterologous GS or GE sequence is of a different RSV gene.

68. (Withdrawn) The recombinant RSV of claim 67, wherein a GE signal of the RSV NS1 or NS2 gene is replaced by a corresponding GE sequence of the RSV N gene.

69. (Withdrawn) The recombinant RSV of claim 66, wherein the heterologous GS or GE sequence is of a heterologous negative stranded virus.

70. (Withdrawn) The recombinant RSV of claim 69, wherein the heterologous GS or GE sequence is of a human RSV A or RSV B subgroup.

71. (Withdrawn) The recombinant RSV of claim 69, wherein the heterologous GS or GE sequence is of a non-human RSV.

72. (Withdrawn) The recombinant RSV of claim 70, wherein the heterologous GS or GE sequence is of a bovine RSV.

73. (Withdrawn) The recombinant RSV of claim 70, wherein the heterologous GS or GE sequence is of a parainfluenza virus (PIV).

74. (Withdrawn) The recombinant RSV of claim 73, wherein the heterologous GS or GE sequence is of a PIV3 virus.

75. (Withdrawn) The recombinant RSV of claim 64, wherein a nucleotide sequence of a gene-start (GS) or gene-end (GE) signal is altered in the genome or antigenome.

76. (Withdrawn) The recombinant RSV of claim 64, wherein a gene-start (GS) or gene-end (GE) signal is rearranged by changing a position of the (GS) or gene-end (GE) signal in the recombinant genome or antigenome.

77. (Cancelled) The recombinant RSV of claim 63, wherein the cis-acting regulatory sequence occurs within a 3' leader, 5' trailer or intergenic region of the RSV genome or antigenome.

78. (Cancelled) The recombinant RSV of claim 77, wherein the cis-acting regulatory sequence is a RSV promoter element.

79. (Cancelled) The recombinant RSV of claim 78, wherein a promoter element is deleted or inserted in the genome or antigenome.

80. (Cancelled) The recombinant RSV of claim 78, wherein a promoter element is substituted in the genome or antigenome by a heterologous promoter element.

81. (Cancelled) The recombinant RSV of claim 80, wherein the heterologous promoter element is of a different RSV gene.

82. (Cancelled) The recombinant RSV of claim 80, wherein the heterologous promoter element is of a heterologous negative stranded virus.

83. (Cancelled) The recombinant RSV of claim 82, wherein the heterologous promoter element is of a human RSV A or RSV B subgroup.

84. (Cancelled) The recombinant RSV of claim 82, wherein the heterologous promoter element is of a non-human RSV.

85. (Cancelled) The recombinant RSV of claim 84, wherein the heterologous GS or GE sequence is of a bovine RSV.

86. (Cancelled) The recombinant RSV of claim 82, wherein the heterologous promoter element is of a parainfluenza virus (PIV).

87. (Cancelled) The recombinant RSV of claim 86, wherein the heterologous promoter element is of a PIV3 virus.

88. (Cancelled) The recombinant RSV of claim 78, wherein a nucleotide sequence of a promoter element is altered in the genome or antigenome.

89. (Cancelled) The recombinant RSV of claim 78, wherein a promoter element is rearranged by changing a position of the promoter element in the recombinant genome or antigenome.

90. (Previously Amended) The recombinant RSV of claim 63, wherein a modification is introduced within the recombinant genome or antigenome comprising a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

91. (Withdrawn) The recombinant RSV of claim 90, wherein a RSV gene is deleted in whole or in part.

92. (Withdrawn) The recombinant RSV of claim 91, wherein a SH, NS1, NS2, or G gene is deleted in whole or in part.

93. (Previously Amended) The recombinant RSV of claim 63, wherein expression of a selected RSV gene is reduced or ablated by introduction of one or more translation termination codons.

94. (Previously Amended) The recombinant RSV of claim 63, wherein expression of a selected RSV gene is reduced or ablated by introduction of multiple translation termination codons.

95. (Withdrawn) The recombinant RSV of claim 90, wherein expression of a selected RSV gene is reduced or ablated by introduction of a frame shift mutation in the gene.

96. (Withdrawn) The recombinant RSV of claim 90, wherein expression of a selected RSV gene is modulated by introduction, modification or ablation of a translational start site within the gene.

97. (Withdrawn) The recombinant RSV of claim 90, wherein a position of one or more gene(s) in the recombinant genome or antigenome is altered relative to a RSV promoter.

98. (Withdrawn) The recombinant RSV of claim 97, wherein said position of said one or more gene(s) is changed to a more promoter-proximal or promoter-distal location by deletion or insertion of a coding or non-coding polynucleotide sequence within the recombinant genome or antigenome upstream of said one or more gene(s).

99. (Withdrawn) The recombinant RSV of claim 97, wherein positions of multiple genes in the recombinant genome or antigenome are altered by changing their relative gene order.

100. (Original) The recombinant RSV of claim 63, wherein the recombinant genome or antigenome is further modified to incorporate one or more attenuating mutation(s) present in one or more biologically derived mutant human RSV strain(s).

101. (Previously Amended) The recombinant RSV of claim 100, wherein the recombinant genome or antigenome is further modified to incorporate at least one and up

to a full complement of attenuating mutations present within a panel of biologically derived mutant human RSV strains, said panel comprising cpts RSV 248 (ATCC VR 2450), cpts RSV 248/404 (ATCC VR 2454), cpts RSV 248/955 (ATCC VR 2453), cpts RSV 530 (ATCC VR 2452), cpts RSV 530/1009 (ATCC VR 2451), cpts RSV 530/1030 (ATCC VR 2455), RSV B-1 cp52/2B5 (ATCC VR 2542), and RSV B-1 cp-23 (ATCC VR 2579).

102. (Withdrawn) The recombinant RSV of claim 100, wherein the recombinant genome or antigenome is further modified to incorporate at least one and up to a full complement of attenuating mutations specifying an amino acid substitution at Val267 in the RSV N gene, Glu218 and/or Thr523 in the RSV F gene, Cys319 Phe 521, Gln831, Met1169, Tyr1321 and/or His 1690 in the RSV polymerase gene L, and a nucleotide substitution in the gene-start sequence of gene M2.

103. (Original) The recombinant RSV of claim 100, wherein the recombinant genome or antigenome incorporates at least two attenuating mutations.

104. (Withdrawn) The recombinant RSV of claim 63, wherein the recombinant genome or antigenome comprises a partial or complete human RSV genome or antigenome of one RSV subgroup or strain combined with a heterologous gene or gene segment from a different, human or non-human RSV subgroup or strain to form a chimeric genome or antigenome.

105. (Withdrawn) The recombinant RSV of claim 104, wherein the heterologous gene or gene segment is from a human RSV subgroup A, human RSV subgroup B, bovine RSV, or murine RSV.

106. (Withdrawn) The recombinant RSV of claim 104, wherein the chimeric genome or antigenome comprises a partial or complete human RSV A subgroup genome or antigenome combined with a heterologous gene or gene segment encoding a RSV F, G or SH glycoprotein or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof from a human RSV B subgroup virus.

107. (Withdrawn) The chimeric RSV of claim 106, wherein both human RSV B subgroup glycoprotein genes F and G are substituted to replace counterpart F and G glycoprotein genes in a partial RSV A genome or antigenome.

108. (Withdrawn) The recombinant RSV of claim 106, wherein the chimeric genome or antigenome comprises a partial or complete human RSV B subgroup genome or antigenome combined with a heterologous gene or gene segment from a human RSV A subgroup virus.

109. (Withdrawn) The recombinant RSV of claim 104, wherein the chimeric genome or antigenome comprises a partial or complete RSV background genome or antigenome of a human or bovine RSV combined with a heterologous gene or genome segment of a different RSV to form a human-bovine chimeric RSV genome or antigenome.

110. (Withdrawn) The recombinant RSV of claim 63, wherein the recombinant genome or antigenome incorporates a heterologous gene or genome segment from parainfluenza virus (PIV).

111. (Withdrawn) The recombinant RSV of claim 110, wherein the gene or genome segment encodes a PIV HN or F glycoprotein or immunogenic domain or epitope thereof.

112. (Withdrawn) The recombinant RSV of claim 110, wherein the genome segment encodes one or more immunogenic protein(s), protein domain(s) or epitope(s) HPIV1, HPIV2, and/or HPIV3.

113. (Withdrawn) The recombinant RSV of claim 63, wherein the recombinant genome or antigenome is further modified to encode a non-RSV molecule selected from a cytokine, a T-helper epitope, or a protein of a microbial pathogen capable of eliciting a protective immune response in a mammalian host.

114. (Previously Amended) The recombinant RSV of claim 63 which is a complete virus.

115. (Original) The recombinant RSV of claim 63 which is a subviral particle.

116. (Previously Amended) The recombinant RSV of claim 63, formulated in a dose of 10^3 to 10^6 PFU of attenuated virus.

117. (Currently Amended) A method for ~~stimulating the~~ eliciting an immune ~~system of an individual to induce protection~~ response in a mammalian subject directed against respiratory syncytial virus, which comprises administering to the ~~individual~~ subject an immunologically sufficient amount of the isolated attenuated recombinant RSV of claim 63.

118. (Previously Amended) The method of claim 117, wherein the recombinant virus is administered in a dose of 10^3 to 10^6 PFU of the attenuated RSV.

119. (Original) The method of claim 117, wherein the recombinant virus is administered to the upper respiratory tract.

120. (Original) The method of claim 119, wherein the recombinant virus is administered by spray, droplet or aerosol.

121. (Original) The method of claim 117, wherein the recombinant virus is administered to an individual seronegative for antibodies to RSV or possessing transplacentally acquired maternal antibodies to RSV.

122. (Currently Amended) ~~A vaccine to induce protection~~ An immunogenic composition effective to elicit an immune response directed against RSV, which comprises an immunologically sufficient amount of the isolated attenuated recombinant RSV of claim 63 in a physiologically acceptable carrier.

123. (Currently Amended) The ~~vaccine~~ immunogenic composition of claim 122, formulated in a dose of 10^3 to 10^6 PFU of the attenuated RSV.

124. (Currently Amended) The ~~vaccine~~ immunogenic composition of claim 122, formulated for administration to the upper respiratory tract by spray, droplet or aerosol.

125. (Withdrawn) The vaccine of claim 122, wherein the recombinant RSV elicits an immune response against human RSV A, human RSV B, or both.

126. (Withdrawn) An expression vector comprising an isolated polynucleotide molecule encoding a respiratory syncytial virus (RSV) genome or antigenome modified by a deletion, insertion, substitution, rearrangement, or nucleotide modification of a cis-acting regulatory sequence.

127. (Previously Amended) An isolated polynucleotide molecule comprising a respiratory syncytial virus (RSV) genome or antigenome which is modified by a deletion, insertion, substitution, rearrangement, or nucleotide modification of a cis-acting regulatory sequence, or by introduction of a translation termination codon.

128. (Withdrawn) The isolated polynucleotide molecule of claim 127, wherein the cis-acting regulatory sequence is a gene-start (GS) signal or a (GE) signal.

129. (Original) The isolated polynucleotide molecule of claim 127, wherein the cis-acting regulatory sequence occurs within a 3' leader, 5' trailer or intergenic region of the RSV genome or antigenome.

130. (Withdrawn) The isolated polynucleotide molecule of claim 127, wherein the cis-acting regulatory sequence is a RSV promoter element.

131. (Original) The isolated polynucleotide molecule of claim 127, wherein a further modification is introduced within the recombinant genome or antigenome comprising a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

132. (Withdrawn) The isolated polynucleotide molecule of claim 131, wherein a RSV gene is deleted in whole or in part.

133. (Original) The isolated polynucleotide molecule of claim 127, wherein expression of a selected RSV gene is reduced or ablated by introduction of one or more translation termination codons in the recombinant genome or antigenome.

134. (Withdrawn) The isolated polynucleotide molecule of claim 127, wherein expression of a selected RSV gene is reduced or ablated by introduction of a frame shift mutation in the gene.

135. (Withdrawn) The isolated polynucleotide molecule of claim 127, wherein expression of a selected RSV gene is modulated by introduction, modification or ablation of a translational start site within the gene.

136. (Withdrawn) The isolated polynucleotide molecule of claim 127, wherein a position of one or more gene(s) in the recombinant genome or antigenome is altered relative to a RSV promoter.

137. (Withdrawn) The isolated polynucleotide molecule of claim 127, wherein the recombinant genome or antigenome is further modified to incorporate one or more attenuating mutation(s) present in one or more biologically derived mutant human RSV strain(s).

138. (Withdrawn) The isolated polynucleotide molecule of claim 137, wherein the recombinant genome or antigenome is further modified to incorporate at least one and up to a full complement of attenuating mutations specifying an amino acid substitution at Val267 in the RSV N gene, Glu218 and/or Thr523 in the RSV F gene, Cys319 Phe 521, Gln831, Met1169, Tyr1321 and/or His 1690 in the RSV polymerase gene L, and a nucleotide substitution in the gene-start sequence of gene M2.

139. (Withdrawn) The isolated polynucleotide molecule of claim 27, wherein the recombinant genome or antigenome comprises a partial or complete human RSV genome or antigenome of one RSV subgroup or strain combined with a heterologous gene or gene segment from a different, human or non-human RSV subgroup or strain to form a chimeric genome or antigenome.

140. (Withdrawn) The isolated polynucleotide molecule of claim 139, wherein the heterologous gene or gene segment is from a human RSV subgroup A, human RSV subgroup B, bovine RSV, or murine RSV.

141. (Withdrawn) The isolated polynucleotide molecule of claim 140, wherein the chimeric genome or antigenome comprises a partial or complete human RSV A subgroup genome or antigenome combined with a heterologous gene or gene segment encoding a RSV F, G or SH glycoprotein or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof from a human RSV B subgroup virus.

142. (Withdrawn) The isolated polynucleotide molecule of claim 141, wherein both human RSV B subgroup glycoprotein genes F and G are substituted to replace counterpart F and G glycoprotein genes in a partial RSV A genome or antigenome.

143. (Withdrawn) The recombinant RSV of claim 127, wherein the recombinant genome or antigenome comprises a partial or complete RSV background genome or antigenome of a human or bovine RSV combined with a heterologous gene or genome segment of a different RSV to form a human-bovine chimeric RSV genome or antigenome.

144. (Withdrawn) The isolated polynucleotide molecule of claim 127, wherein the recombinant genome or antigenome incorporates a heterologous gene or genome segment from parainfluenza virus (PIV).

145. (Withdrawn) The isolated polynucleotide molecule of claim 27, wherein the recombinant genome or antigenome is further modified to encode a non-RSV molecule selected from a cytokine, a T-helper epitope, or a protein of a microbial pathogen capable of eliciting a protective immune response in a mammalian host.

146. (Cancelled) A method for producing an infectious respiratory syncytial virus RSV) particle from one or more isolated polynucleotide molecules encoding said RSV particle from one or more isolated polynucleotide molecules encoding said RSV comprising:

expressing in a cell or cell-free lysate an expression vector comprising an isolated polynucleotide comprising a recombinant RWSV genome or antigenome which is

modified by a deletion, insertion, substitution, rearrangement, or nycleotide modification of a cis-acting regulatory sequence, or by introduction of a translation termination codon.

147. (Cancelled) The method of claim 146, wherein the recombinant RSV genome or antigenome and the N,P,L and RNA polymerase elongation factor proteins are expressed by two or more different expression vectors.